(b) resistant to exposure to drying;

(c) resistant to exposure to lytic agents;

(d) resistant to exposure to mutator hosts;

(e) resistant to heat shock; and

(f) resistant to resistant to ionic variation.

REMARKS

Claims 23-33, 35-47, 49, and 50 are now pending in this application. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the reasons which follow.

I. Summary of the Claimed Invention

The claimed invention is directed to methods of treating mammals suffering from a bacterial infection with a bacteriophage composition comprising a bacteriophage preparation that is purified, host-specific, non-toxic, virulent, and has a wide host range. *See e.g.*, page 1, lines 4-6; and page 4, lines 14-16, of the application. The preparation consists essentially of two or more phage strains that are each host-specific in that they are selected against a particular bacteria group. Each phage strain has a wide host range in that it is effective in killing, *in vitro*, bacteria from at least 50% of bacterial isolates from the same bacterial strain that it was isolated from.

II. Rejections under 35 U.S.C. § 112, ¶ 2

Claims 23, 33, and 47 were rejected under 35 U.S.C. § 112, ¶ 2, for alleged indefiniteness. With regard to claim 23, the examiner alleged that the relationship between the bacterial infection treated and the phages administered is unclear. Claim 23 has been amended to clarify that the administered phage strain is specific for the bacterial infection treated. Withdrawal of this ground for rejection is respectfully requested.

With regard to claims 33 and 47, the examiner alleged that it is unclear which component of the "preparation" provides resistance to the enumerated environmental conditions—the phage or the carrier. Applicants respectfully traverse this rejection. Claim 33 and 47 depend from claims 24 and 46, respectively, which in turn depend from claims 23 and 37, respectively. Claims 23 and 37 both clearly state that composition comprises two components: (a) the phage "preparation", and (b) a pharmaceutically acceptable carrier. It is therefore clear from the antecedent use of the term "preparation" in the claim that it is the phage itself which is resistant to one or more of the enumerated environmental conditions. *See* page 5, lines 24-30; page 7, lines 4-10; page 11, lines 19-22; page 14, lines 7-24; and page 21, lines 6-12 for further discussion and explanation. Nonetheless, applicants have amended these claims to further clarify that the "bacteriophage preparation" provides the resistance. Withdrawal of this ground for rejection is respectfully requested.

III. Rejections under 35 U.S.C. § 102

A. Merril et al., U.S. Patent No. 5,688,501

The examiner maintained the previous rejection of claims 23-25, 29-30, 33-39, 43-44, and 47-50 under 35 U.S.C. § 102(e) as being allegedly anticipated by Merril et al., U.S. Patent No. 5,688,501. Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis for Rejection

The examiner maintained that Applicants have defined the term "wide host range" to mean two or more phage strains and that Merril et al. discloses a lambda phage composition that would specifically interact with multiple strains of *E. coli*. The examiner also maintained that Merril et al. "teaches through citing" two Zhurnal Mikrobiologii articles the utilization of polyvalent phage preparations that contain phages for multiple species of Klebsiella. It is the examiner's position that Merril et al. therefore teaches a phage preparation

containing wide host range because it discloses a preparation containing a plurality of strains of phage.

2. The Examiner Misunderstands the Meaning of "Host Range"

Applicants respectfully submit that the examiner's statement that applicants define the phrase "wide host-range" in the claims to mean a phage preparation having at least two or more phage strains is incorrect. The phrase "wide host range" is defined in the specification to refer to a characteristic of a phage strain in which the phage is effective in killing a wide range of isolates from a single bacterial group. Applicants direct the examiner to page 8, ¶ 1 of the specification:

> [T]he expression "wide host range" denotes a bacteriophage that is capable of killing bacteria from a variety of different hosts. Preferably, the bacteriophage of the present invention are capable of killing bacteria from at least 50% of the host samples. Throughout this description, the term "virulent" denotes a bacteriophage that is capable of effectively killing bacteria from a wide host range. Preferably, the bacteriophage that are selected are effective in killing about 100% more bacteria from various sources, or hosts, when compared to the bacteriophage that are not selected. More preferably, the bacteriophage are selected that kill about 200% more bacteria, and most preferably, bacteriophage are selected that kill about 300% more bacteria. Fore example, by means of illustration only, assume two bacteriophage preparations are selected and each are tested against bacteria samples from 100 different hosts. If the first one is effective in killing 15 hosts, and the second is effective in killing bacteria from 60 hosts, then the second bacteriophage preparation would be virulent and would have a wider host range, and the second bacteriophage preparation would kill [stet] 300% more bacteria than the first.

Applicants also direct the examiner to page 26, Example 9, wherein *S. Aureus* phage strain 83A was compared to another *S. Aureus* phage strain in nine different host samples of *S. Aureus*. Phage 83A was effective in killing five of nine (56%) isolates whereas the other phage was effective in killing only one of nine (11%). "Thus 83A bacteriophage had a wider host range than and killed

400% more bacteria." Lastly, applicants direct the examiner's attention to the *Academic Press Dictionary of Science and Technology* ("**host range.** *Virology*, the collection of all species of hosts that are susceptible to infection with a given virus."). Thus, this term clearly does not refer to the number of phage strains but rather the ability of a given phage strain to kill many bacteria isolates.

Applicants direct the examiner to claim 23, limitation (a)(3) as the limitation that corresponds to the wide host range characteristic of the phage preparations used in the claimed invention:

> "each bacteriophage is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, wherein the isolates are from the same strain of bacterial organism from which the bacteriophage strain is isolated"

Contrary to the examiner's understanding, therefore, claim 23, limitation (a)(1)'s requirement that the preparation "consist essentially of two or more bacteriophage strains" does not correspond to the wide host range characteristic of the claimed composition. The corresponding limitation is (a)(3).

3. Merril et al. Does not Disclose a Bacteriophage Preparation Having a Wide Host Range

Merril et al. sought to develop a phage that would be more effective in treating a bacterial infection by making a phage that would be resistant to inactivation by the treated animal's host defense system, which Merril et al. measured by the half-life of the phage in the animal's body. Resistance to inactivation is the defining characteristic of Merril et al. Specifically, Merril et al. discloses two methods for making a phage strain with a longer survival rate in the body than wild-type phage: a "serial passage" method and a "genetic engineering" method. Since the examiner appears to believe that the "serial passage" method anticipates applicant's claims, applicant's remarks will be so limited. In the "serial passage" method, a phage strain is injected into a mouse and the titer of the phage is monitored. When the titer reaches a range of 0.01-1%, the remaining phage (which has survived the longest in the body) is isolated and plaque purified. The process is repeated until a phage is obtained that can

survive at least as long in the body than the longest-surviving wild-type phage. *See* col. 3, lines 52-56. Thus, Merril et al.'s selection system is based on longevity/survival of the phage in the body. Merril et al. also state that the phage can be subjected to mutagens before injection in the hope of provoking a mutation that imparts the desired resistance to inactivation. *See* col. 5, lines 32-47.

Applicants direct the examiner's attention to the discussion on page 3, ¶ 1, of the present application, where it is stated that the serial passage method may produce a phage with a longer circulation in the body, but that longer circulation does not preclude the phage from being less virulent and therefore ineffective as a treatment.

Applicants sought to develop a phage composition having improved virulence as measured by the number of bacteria the phage can infect (host range) and by the phage's resistance to certain harsh conditions. See p. 5, lines 19-24:

> bactriophages can be selected which... are capable of killing a wider range of host bacteria from a wider range of different isolated cultures of a given bacteria, i.e., a wide host range. Other techniques useful for selecting bacteria include selecting those that: (i) are resistant to exposure to high temperatures or drying; (ii) are resistant to exposure to lytic agents or mutator hosts; (iii) survive for a period of time greater than 24 hours under normal or abnormal conditions; (iv) are resistant to heat shock; and/or (v) are resistant to ionic variation including drying, overhydration or extremes of individual ionic concentrations.

Applicant's phage selection system is based not on longevity in the body like Merril et al., but rather on in vitro host range measurements and also resistance to the environmental conditions enumerated in the dependent claims.

Merril et al. does not address or even discuss the development of a phage that has the wide host range and resistance to environmental conditions characteristics of the claimed invention. Contrary to the examiner's contentions, Merril et al. does not disclose a phage preparation having a wide host range at cols. 13 and 14. Although Merril et al. discloses lambda phage generally, it does not disclose a lambda phage that is effective in killing, *in vitro*, *E. coli* from at

least about 50% of *E. coli* isolates, wherein the isolates are from the same strain of *E. coli* from which the lambda phage strain was isolated, as required by the claims.

The examiner's citation to the two Zhurnal Mikrobiologii references cited in Merril et al. also does not show anticipation. First, those references were described as being part of the prior art, and simply did not relate to Merril et al.'s invention. A reference cited in a patent cannot become part of the patented invention merely by citation to it, unless, *perhaps*, the patent somehow affirmatively states that the reference describes some feature of the invention, which Merril et al. does not.

Second, neither of the Zhurnal Mikrobiologii reference anticipate the claims because neither reference describes a phage with a wide host range as defined by applicants. The fact that the abstracts describe polyvalent phage preparations does not show that the preparations had a wide host range. Nowhere do the abstracts describe how the phages were prepared and whether they were tested against isolates from the bacteria from which they were isolated. The references do not disclose a phage that was effective in killing, *in vitro*, bacteria from at least about 50% of bacteria isolates, wherein the isolates are from the same strain of bacteria from which it was isolated, as required by the claims.

4. Merril et al. does not teach a composition comprising two or more bacteriophage strains

Merril et al. does not anticipate the claims for the further reason that it does not teach a composition comprising two or more phage strains. Merril et al. only discussed the isolation and use of a single phage strain.

5. Merril et al. does not teach a purified, non-toxic phage preparation

Lastly, Merril et al. does not anticipate the claims because it does not teach a purified, non-toxic phage preparation, as defined by the applicants on page 9, ¶ 2: "[P]urified" denotes a phage preparation that contains substantially no toxins (no endotoxins), preferably less than 1.0% by weight of toxins (endotoxins) and more preferaby less than 0.05% by weight of toxins (endotoxins)." Merril et al. nowhere discusses removal of endotoxins from the phage preparation.

6. Conclusion

For the foregoing reasons, Merril et al. does not disclose each and every one of the limitations of the claimed invention. Withdrawal of this anticipation rejection is therefore respectfully requested.

B. Norris, U.S. Patent No. 4,957,686

The examiner has also maintained her previous rejection of claims 23, 24, 33, 34, 37, 38, 47, and 48 under 35 U.S.C. § 102(b) as being allegedly anticipated by Norris, U.S. Patent No. 4,957,686. Applicants again respectfully traverse this ground for rejection.

1. The Examiner's Basis for Rejection

In support of this ground for rejection, the Examiner stated that Norris discloses the administration of a mixture of phages specific for different *Streptococcus* strains, with a pharmaceutically acceptable carrier.

2. Norris also Does not Disclose a Bacteriophage Preparation Having a Wide Host Range

Norris discloses using a phage against *Streptococcus sanguis* in the mouth, optionally in conjunction with different phages parasitic to other bacteria found in the mouth. *See* col. 3, lines 46-53. Norris does not disclose that any of the phages utilized in this method have a wide host range as defined by applicants and discussed extensively above. Specifically, Norris does not state or suggest that the phage is effective in killing, *in vitro*, bacteria from at least about 50% of bacteria isolates, wherein the isolates are from the same strain of bacteria as that from which the phage was isolated, as required by the claims. Rather, Norris contemplates that different phages for different bacteria are used. *See id.* Norris also nowhere discloses that the phages are resistant to the environmental conditions enumerated in the claims. Because Norris does not disclose each and every one of the limitations of the claimed invention, withdrawal of the anticipation rejection is respectfully requested.

IV. Rejections under 35 U.S.C. § 103

A. Merril et al., U.S. Patent No. 5,688,501, and Denney, U.S. Patent No. 3,793,151

Claims 26 and 40 were rejected under 35 U.S.C. § 103 as being allegedly obvious over Merril et al., U.S. Patent No. 5,688,501, for reasons discussed above, in view of Denney, U.S. Patent No. 3,793,151, which is alleged to disclose a phage specific to *S. pyrogenes*. The examiner also alleged that Merril et al. discloses a bacteriophage that has the capacity to kill at least 50% of bacteria in an *in vitro* assay based on statements in the specification regarding an LD50 dose of bacteria.

Applicants respectfully traverse this ground for rejection. Applicants respectfully submit that the examiner has mistakenly equated Merril et al.'s

disclosure regarding an LD50 dose of bacteria to mice with the concept of a wide host-range phage in applicants' invention.

As discussed above, In Merril et al.'s "serial passage" method, a phage strain is injected into a mouse and the titer of the phage is monitored. When the titer reaches a range of 0.01-1%, the remaining phage (which has survived the longest in the body) is isolated and plaque purified. The process is repeated until a phage is obtained that can survive at least as long in the body than the longest-surviving wild-type phage. *See* col. 3, lines 52-56.

In example 3 (col. 11-12), Merril et al. gives a prophetic test for determining whether a lambda phage made from this process (anti-HDS selected phage lambda) is more effective than wild-type phage. Accordingly, Merril et al. compared the anti-HDS phage with the wild-type phage by administering an LD50 dosage of E. coli to mice either I.P. or I.V. and then administering either $1x10^{12}$ anti-HDS phage, wild-type phage, or saline. There are no results disclosed in the example. Merril et al. also gives a prophetic test for determining the efficacy of the genetically engineered phage in example 6 (col. 14-15).

The LD50 dosage in Merril et al. refers to the dose of *bacteria* administered to the *mouse* and has nothing to do with the *phage* preparation. "LD50" refers to the toxicity of a material. "LD" refers to "lethal dose". "LD50" is the *amount, or dosage,* of a material, necessary to kill 50% of the experimental subjects. *See* Life Science Dictionary (attached): ("**lethal dose 50 (LD50, median lethal dose)** The amount, or dosage, of a toxin necessary to kill 50% of the experimental subjects"). All Merril et al. stated was that a particular dosage—an LD50 dose—of *E. coli* was administered to the mouse. This did not relate to any characteristic of the phage disclosed in the reference, and does not indicate that the phage administered had a wide host range as defined by applicants and discussed extensively above. In fact, the examples are merely prophetic, and no results are given.

Denny does not remedy the deficiencies of Merril et al. Denny isolated a phage capable of infecting and lysing only non-encapsulated *S. pyogenes*. Col. 2, line 56 to col. 4, line 10. Denny does not disclose a phage with a wide host range as defined by applicants, a non-toxic phage, or administration of 2 phage

strains to a mammal suffering from bacterial infection. The combination of Merril et al. and Denny therefore do not render the claims obvious. Accordingly, withdrawal of this ground for rejection is respectfully requested.

B. Merril et al., U.S. Patent No. 5,688,501, and He et al., 1992 (Abstract)

Claims 27 and 41 were rejected under 35 U.S.C. § 103 as being allegedly obvious over Merril et al., U.S. Patent No. 5,688,501, for reasons discussed above, in view of He et al., 30 *J. Clin. Microbiol.* 590 (1992) (Abstract), which allegedly discloses a phage specific to *Citrobacter freundii*. Applicants respectfully traverse this ground for rejection.

He does not remedy the deficiencies of Merril et al. discussed above. He et al. isolated three phages specific for *C. freundii* as well as phages for other bacteria found in sewage and used the phages for a diagnostic typing of bacteria. He et al. does not disclose a phage with a wide host range as defined by applicants, a non-toxic phage, or administration of two phage strains to a mammal suffering from bacterial infection. The combination of Merril et al. and He et al. therefore do not render the claims obvious. Accordingly, withdrawal of this ground for rejection is respectfully requested.

C. Merril et al., U.S. Patent No. 5,688,501, and Sekaninova et al, 1995 (Abstract)

Claims 28 and 42 were rejected under 35 U.S.C. § 103 as being allegedly obvious over Merril et al., U.S. Patent No. 5,688,501, for reasons discussed above, in view of Sekaninova et al., 3(2) *Cent. Eur. J. Pub. Health* 80 (1995) (Abstract), which is alleged to disclose a phage specific to *Klebsiella oxytoca*. Applicants respectfully traverse this ground for rejection.

Sekaninova does not remedy the deficiencies of Merril et al. discussed above. All that the Sekaninova abstract states with regard to *K. oxytoca* is that it was "identically sensitive to some of the phages 1, 2, 3, 8, and 106, particularly to phages 2 and 3, or 2, 3, and 106." These phages are not further

discussed in the abstract. Sekaninova does not disclose a phage with a wide host range as defined by applicants, a non-toxic phage, or administration of two phage strains to a mammal suffering from bacterial infection. The combination of Merril et al. and Sekaninova therefore do not render the claims obvious. Accordingly, withdrawal of this ground for rejection is respectfully requested.

D. Merril et al., U.S. Patent No. 5,688,501, and Bar-Shalom et al., U.S. Patent No. 5,213,808

Claims 31 and 45 were rejected under 35 U.S.C. § 103 as being allegedly obvious over Merril et al., U.S. Patent No. 5,688,501, for reasons discussed above, in view of and Bar-Shalom et al., U.S. Patent No. 5,213,808, which is alleged to disclose liposomes as a means for delivering an active agent to a mammal. Applicants respectfully traverse this ground for rejection.

Bar-Shalom et al. does not remedy the deficiencies of Merril et al. discussed above. Bar-Shalom discloses a "controlled release article with pulsatile release." The controlled release composition disclosed in Bar-Shalom is not a liposome. All that Bar-Shalom states is that the controlled-release composition can be employed to deliver a number of active agents, including (a) bacteriophages and (b) active agents in liposomes. Col. 9, line 45-57. Contrary to the examiner's allegation, Bar Shalom does not state or suggest delivering a bacteriophage in a liposome, but rather a bacteriophage or an active agent in a liposome in the disclosed controlled-release formulation. Bar-Shalom et al. also does not disclose a phage with a wide host range as defined by applicants, a non-toxic phage, or administration of 2 phage strains to a mammal suffering from bacterial infection. The combination of Merril et al. and Bar Shalom therefore do not render the claims obvious. Accordingly, withdrawal of this ground for rejection is respectfully requested.

E. Merril et al., U.S. Patent No. 5,688,501, and Tomalia et al., U.S. Patent No. 5,714,166

Claims 31 and 45 were rejected under 35 U.S.C. § 103 as being allegedly obvious over Merril et al., U.S. Patent No. 5,688,501, for reasons discussed above, in view of and Tomalia et al., U.S. Patent No. 5,714,166, which is alleged to disclose dendrimers as a means for delivering high concentrations of phage. Applicants respectfully traverse this ground for rejection.

Tomalia et al. does not remedy the deficiencies of Merril et al. discussed above. Tomalia discloses dense star polymers, called STARBURST™ polymers, for delivering high concentrations of materials such as phages. Col. 1, lines 45-53 and col. 2, lines 10-20. Contrary to the examiner's suggested equation of dense star polymers and liposomes, they are not the same. See col. 15, lines 47-57, which states as follows:

> Thus, at G = 9.0, the STARBURST™ PAMAM is behaving topologically like a vesicle (liposome). However, this STARBURST™ is an order of magnitude smaller and very monodispersed compared to a liposome and is much more physically stable than a liposome. Consequently, the present dendrimers have a large enough void interior to molecularly encapsulate solvent filled void spaces of as much diameter as about 63 Å (volume about 131,000 $Å^3$) or more. These micelle sized prototypes appear to behave like a covalently fixed liposome at this advanced generation stage.

Tomalia therefore does not state or suggest delivering a bacteriophage in a liposome. Tomalia also does not disclose a phage with a wide host range as defined by applicants, a non-toxic phage, or administration of 2 phage strains to a mammal suffering from bacterial infection. The combination of Merril et al. and Tomalia therefore do not render the claims obvious. Accordingly, withdrawal of this ground for rejection is respectfully requested.

V. Conclusion

In light of the foregoing amendments and arguments, Applicants believe that the present application is now in condition for allowance. Favorable

reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date Sept 5, 2002 By Michele M Simkin

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Twice Amended) A method of treating a mammal suffering from bacterial infection comprising administering to the mammal an effective amount of a composition comprising:

(a) a purified, host-specific, non-toxic, wide host-range, and virulent bacteriophage preparation, wherein:

(1) the bacteriophage preparation consists essentially of two or more bacteriophage strains, wherein each bacteriophage strain is specific for the bacterial infection treated and is selected against one of the group consisting of staphylococci, hemophilii, helicobacter, mycobacterium, mycoplasmi, streptococci, neisserii, klebsiella, enterobacter, proteus, bacteriodes, pseudomonas, borrelii, citrobacter, escherichia, salmonella, propionibacterium, treponema, shigella, enterococci, and leptospirex;

(2) at least two of the bacteriophage strains are isolated against different strains of bacterial organisms; and

(3) each bacteriophage strain is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, wherein the isolates are from the same strain of bacterial organism as that from which the bacteriophage strain is isolated; and

(4) the bacteriophage preparation can be safely administered to patients or mammals in need; and

(b) a pharmaceutically acceptable carrier.

33. (Once Amended) The method of claim 24, wherein the bacteriophage preparation is resistant to one or more properties selected from the group consisting of:

(a) resistant to exposure to high temperatures;

(b) resistant to exposure to drying;

(c) resistant to exposure to lytic agents;

(d) resistant to exposure to mutator hosts;

(e) resistant to heat shock; and

(f) resistant to resistant to ionic variation.

47. (Once Amended) The method of claim 38, wherein the bacteriophage preparation is resistant to one or more properties selected from the group consisting of:

(a) resistant to exposure to high temperatures;

(b) resistant to exposure to drying;

(c) resistant to exposure to lytic agents;

(d) resistant to exposure to mutator hosts;

(e) resistant to heat shock; and

(f) resistant to resistant to ionic variation.